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Title

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Presentation Information

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Keywords

COVID-19, SARS-CoV-2, Acute limb ischemia, coronavirus, arterial thromboembolism

Conflicts of Interests

None

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ARTICLE HIGHLIGHTS

Type of Research: Multicenter, retrospective, propensity score-matched study

Key Findings: Acute limb ischemia (ALI) patients with COVID-19 (n=526) were compared to those without COVID-19 (n=14131). After propensity matching, ALI patients with COVID-19 had a higher mortality rate (24.857% vs 9.178%; p<0.0001), MALE (5.763% vs 2.868%; p=0.0223), and acute renal failure (22.180% vs 14.914%; p<0.0001).

Take home Message: These findings suggest that ALI patients with COVID-19 have significantly different patient demographics and comorbidities than both classical ALI patients and COVID-19 patients without ALI and experienced higher rates of adverse clinical outcomes than ALI patients without COVID-19.

Table of Contents Summary

In this retrospective study, patients who had acute limb ischemia with COVID-19 were observed to have worse clinical outcomes compared to patients with ALI or COVID-19 infection alone. The presence of comorbidities such as hypertension and diabetes mellitus prior to SARS-CoV-2 infection may significantly worsen outcomes related to ALI.

ABSTRACT

Introduction/Objective

The inflammatory cascade caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may result in arterial thrombosis and acute limb ischemia (ALI) with devastating consequences. The aims of this study were to compare outcomes of ALI in the lower

extremities in patients with and without COVID-19, and to determine if ALI development in the context of COVID-19 portends a worse prognosis compared to COVID-19 without ALI.

Methods

Queries were built on TriNetX, a federated network of healthcare organizations (HCOs) across the United States that provides de-identified patient data. ICD-10 diagnostic codes were used to identify patients with acute limb ischemia of the lower extremities and COVID-19. The study timeframe was defined as January 20, 2020-May 20, 2021. Statistical analyses, including propensity score matching, were done through TriNetX's internal software. Outcomes looked at are rates of mortality, stroke, myocardial infarction, major adverse limb events, re-intervention, respiratory failure, sepsis, mental health complications, and acute renal failure. Baseline cohort characteristics were also collected.

Results

ALI patients with COVID-19 (ALI C19+; n=526) were significantly less likely than ALI patients without COVID-19 (ALI; n=14131) to have baseline comorbidities, including nicotine dependence (18% vs 33%; p<0.0001). In contrast, ALI C19+ patients had significantly more comorbidities than hospitalized COVID-19 patients without ALI (n=275903), including nicotine dependence (18% vs 10%; p<0.0001). After propensity matching was performed, ALI C19+ patients had significantly higher rates of mortality (24.9% vs 9.2%; p<0.0001), major adverse limb events (5.8% vs 2.9%; p=0.0223), and acute renal failure (22.2% vs 14.9%%; p=0.0025) than ALI patients. Compared to hospitalized COVID-19 patients without ALI, ALI C19+ patients had higher propensity-matched rates of respiratory failure and being placed on assisted ventilation (32.9% vs 27%; p=0.0369), sepsis (16.9% vs 12.2%; p=0.0288), acute renal failure (22.1% vs 14.6%; p=0.0019), and mortality (24.7% vs 14.4%; p<0.0001).

Conclusions

Patients who developed ALI following COVID-19 present with significantly different demographics and comorbidities from those who develop ALI without COVID-19. After controlling for these variables, higher rates of major adverse limb events, acute renal failure, and mortality in ALI patients with COVID-19 suggest that not only may COVID-19 precipitate ALI, but it may also exacerbate ALI sequelae. Furthermore, development of ALI in COVID-19 portends worse prognosis compared to COVID-19 patients without ALI.

INTRODUCTION

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in the United States on January 20, 2020, progress has been made in understanding its pathogenicity.

Current understanding of SARS-CoV-2 has proposed that it binds to angiotensin-converting enzyme 2 (ACE-2) receptors, causing significant inflammation. SARS-CoV-2 bound to these receptors on vascular endothelial cells causes endothelial injury and triggers a pro-inflammatory and hypercoagulable state.[1] Abdominal and thoracic aortic thrombosis, mesenteric ischemia, and acute cerebrovascular incident have also been described as manifestations of COVID-19 infection.[2] Acute limb ischemia (ALI), a vascular pathology with multifactorial etiology, is a known complication caused by the inflammatory cascade triggered by SARS-CoV-2 viral infection.[3,4] Although hypercoagulability is a rare cause of limb ischemia, the incidence of thromboembolic events in COVID-19 patients is as high as 35% to 45%.[5] Several observational studies have found that patients with COVID-19 and ALI experience poor outcomes, including high rates of amputation and high failure rates of revascularization.[3,4] However, the

characteristics of patients presenting with ALI following COVID-19 compared to characteristics of patients presenting with ALI alone have not been delineated. Furthermore, the degree to which COVID-19 exacerbates ALI sequelae, and the prognostic value of ALI development in COVID-19 compared to COVID-19 alone, has not been shown. As such, the purpose of this multicenter, retrospective cohort study was to compare the outcomes of ALI in COVID-19 patients to ALI patients without COVID-19.

METHODS

Data source

Data for this study was obtained from TriNetX's COVID-19 Research Network platform, a federated research network of electronic health record (EHR) data from 63 healthcare organizations (HCOs) across the United States. The network provides access to real-time aggregate data from approximately 83.8+ million patients including demographics, diagnoses, procedures, medications, lab values, and genomics. The HCOs that comprise the research network include primary care providers, specialists, and hospitals that care for both insured and uninsured patients. The geographical distribution of patients in the database are as follows: 18% from the Northeast, 14% from the Midwest, 26% from the South, and 30% from the West.

Any data on the TriNetX platform in aggregate form only contains de-identified data, adhering to the standard defined in Section §164.514(a) of the HIPAA Privacy Rule. TriNetX's de-identification process was attested through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule, superseding the need for TriNetX's previous waiver from the Western Institutional Review Board.[6] Written patient consent was waived. Because this study was not involved in the collection, use, or transmittal of

individually identifiable data, this study was exempted from Albert Einstein College of Medicine and Montefiore Medical Center Institutional Review Board approval. This multicenter, retrospective cohort study followed the RECORD guidelines.[7]

Study protocol

The study timeframe was defined as January 20, 2020, to May 20, 2021. The first reported case of SARS-CoV-2 in the United States was on January 20, 2020, and the first reported case of the Delta variant in the United States was towards the end of May 2021.[8,9] The emergence of the Delta variant was set as the end point of the study because of its markedly different pathogenicity from its parent strains.[8]

International Classification of Diseases, Tenth Revision (ICD-10) codes were used to identify eligible patients as seen in supplementary table I. ICD-10 codes were linked to the dates the events occurred. Mainly, ALI of the lower extremities was defined as thrombosis of the arteries of the lower extremities (I74.3), iliac artery (I74.5), or saddle embolus of the abdominal aorta (I74.01). COVID-19 positivity was defined as having a record of a positive SARS-CoV-2 test (9088) or diagnosis of COVID-19 (U07.1). Furthermore, patients were identified as having COVID-19 if they had records of unspecified coronavirus infection within the study timeframe (B34.2), pneumonia due to SARS-associated coronavirus (J12.81), and coronavirus as the cause of diseases classified elsewhere (B97.29). Previous EHR studies on COVID-19 included the latter ICD-10 codes (i.e., B34.2, J12.81, B97.29) because there was no established code for COVID-19 early in the pandemic.

COVID-19 patients who developed ALI (ALI C19+) were identified by looking at the temporal relationship between the ICD-10 codes for ALI and COVID-19. Namely, these patients must have had a diagnosis of ALI either one day before, or within one week after COVID-19

diagnosis/positivity. This temporal relationship was decided upon because a prior study found ALI to develop around one week after COVID-19.[10] Furthermore, patients may have had an incidental COVID-19 finding if they were initially admitted for ALI, hence including patients with diagnosis of ALI one day before COVID-19 diagnosis/positivity. Patients who developed ALI without concurrent COVID-19 were identified by excluding all patients who had a record of COVID-19. This meant that patients who had COVID-19 months prior to diagnosis of ALI were also excluded, reasoning that the long-term effects of COVID-19 have not been fully studied. Patients who were hospitalized for COVID-19 and did not develop ALI were identified by excluding any instance of ALI after COVID-19 diagnosis, again reasoning that the long-term effects of COVID-19 have not been fully studied.

The ALI C19+, and ALI without COVID-19 cohorts were stratified into those who had an arterial revascularization procedure performed, and those who did not. Arterial revascularization procedures included endovascular, bypass, and embolectomy/thrombectomy/endarterectomy techniques (supplementary table I). We defined late surgical intervention as patients who did not have record of intervention within one week of ALI, but subsequently had an intervention during the follow-up period of 180 days. Because this was a rare outcome, we defined late surgical intervention as a composite of endovascular, bypass, and embolectomy/ thrombectomy/ endarterectomy techniques (supplementary table I). The follow-up period was defined as 180 days, and outcomes followed were mortality, stroke, myocardial infarction, major adverse cardiovascular events (MACE; composite of mortality, stroke, myocardial infarction), major adverse limb events (MALE; amputations), acute renal failure, re-intervention rates, respiratory failure or assisted ventilation, sepsis, and mental health complications (supplementary table I).

Statistical methods

All statistical analyses, including 1:1 propensity score matching, were performed with TriNetX's internal software, which uses R 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and Python 3.6.5 (Python Software Foundation, Centrum voor Wiskunde en Informatica Amsterdam, The *Netherlands*). Greedy nearest neighbor matching with a caliper width of 0.1 pooled standard deviations of the logit of the propensity scores in aggregate was used; standard difference less than 0.1 was considered well match.[11] Propensity matching was performed for age, sex, ethnicity, medications, and comorbidities (Supplementary table II). Propensity score distributions before and after matching were reported (Figures I and II). Descriptive statistics were expressed as means with standard deviations. Unpaired t-tests were used to compare means between the cohorts. Odds ratios with 95% confidence intervals (CI) were reported, and p-values <0.05 were considered statistically significant.

RESULTS

Characteristics of ALI C19+ patients compared to ALI patients without C19

A total of 526 patients were identified in the group with acute limb ischemia with COVID-19 and 14,131 in the group with acute limb ischemia without COVID-19 (Table I). 120 patients who had ALI following COVID-19 were not included because they did not meet the one-week criteria. Unpaired t-tests were performed between the two cohorts. The mean age for the groups was similar (65.2+/-14.7 vs 65.6+/-13.8, p=0.5109). The gender distribution was not statistically different between the two groups (64% vs 59% male, p=0.0534). Interestingly, there was a higher proportion of Hispanic patients in the ALI C19+ group (11% vs 4%, p<0.0001) and a higher proportion of Caucasian patients in the COVID-19 negative group (64% vs 69%,

p=0.0052). There was no difference in the proportion of African Americans between the two groups (16% vs 13%, p=0.0508).

There were many significant differences in baseline comorbid conditions between these two groups. Primary hypertension (51% vs 60%, p<0.0001), Chronic Ischemic Heart Disease (28% vs 37%, p=0.0001), COPD (14% vs 20%, p=0.0004), psychiatric disorders (42% vs 50%, p=0.0004), and neoplasms (19% vs 27%, p<0.0001) were all seen at significantly higher rates in ALI patients without COVID-19. In the ALI patients with COVID-19, significantly increased rate of Type 2 Diabetes Mellitus (34% vs 30%, p=0.0420) was seen. Nicotine dependence was seen at a 2-fold higher rate in ALI patients without COVID-19 (18% vs 33%, p<0.0001).

ALI patients without COVID-19 were more likely to be on baseline aspirin (35% vs 49%, p<0.0001, atorvastatin (29% vs 38%, p<0.0001), ACE inhibitors (20% vs 29%, p<0.0001), and beta blockers (41% vs 49%, p=0.0003).

Outcomes of ALI C19+ patients compared to those without COVID-19

Propensity matching was performed in addition to unpaired t-tests. Before propensity matching, patients with COVID-19 and ALI had worse outcomes at 180 days (Table II). There was a 3-fold increase in mortality (24.715% vs 8.598%, OR 3.490, p<0.0001), a 2-fold increase in MALE (5.894% vs 2.696%, OR 2.260, p<0.0001), and a 2.5-fold increase in acute renal failure (22.053% vs 13.347%, OR 1.837, p<0.0001) in the ALI C19+ group. This trend remained significant after propensity matching with a 3-fold increase in mortality (24.857% vs 9.178%, OR 3.273, p<0.0001), 2-fold increase in MALE (5.763% vs 2.868%, OR 2.061, p=0.0223), and nearly 2-fold increase in acute renal failure (22.180% vs 14.914%, OR 1.626, p=0.0025).

Outcomes for ALI C19+ Patients Versus Those with ALI Alone Undergoing Arterial Procedures

Unpaired t-tests, without propensity matching, were performed. After propensity matching, there were too few patients remaining in the ALI C19+ group for adequate statistical comparison. There was a small proportion of patients in each group that initially underwent arterial procedures in this subset, with 89 patients in the ALI C19+ group and 2,768 patients in the ALI group (Table III).

ALI C19+ patients were seen to have significantly higher rates of MALE (15.730% vs 8.020%, OR 2.141, p=0.0093) and acute renal failure (22.472% vs 14.884%, OR 1.510, p=0.0492). Open reintervention with thromboendarterectomy, embolectomy, and/or thrombectomy was over 8-fold higher in ALI patients with COVID-19 (31.461% vs 4.986%, OR 8.748, p<0.0001). Reintervention with bypass surgery was also seen at a significantly higher rate in ALI C19+ (11.236% vs 5.636%, OR 2.119, p=0.0262). There was no statistically significant difference in the rate of endovascular reintervention between the two groups.

Outcomes for ALI C19+ Patients Who Did Not Undergo Arterial Procedures

Unpaired t-tests, without propensity matching, were performed. After propensity matching, there were too few patients remaining in the ALI C19+ group for adequate statistical comparison. MACE was seen at a greater than two-fold higher rate in the ALI C19+ group who did not undergo arterial interventions (33.410% vs 16.700%, OR 2.503, p<0.0001) (Table IV). In COVID-19 patients without initial revascularization, there were significantly higher rates of MALE (3.432% vs 1.356%, OR 2.586, p=0.0003), acute renal failure (21.739% vs 12.756%, OR 1.900, p<0.0001). Interestingly, there was a significantly lower rate in ALI C19+ patients needing surgical intervention later (2.746% vs 5.573%, OR 0.478, p=0.0108).

Characteristics of ALI C19+ patients compared to hospitalized C19+ patients without ALI

Unpaired t-tests were performed between the two cohorts. When compared to hospitalized C19+ patients who did not develop ALI (n=275,903), ALI C19+ patients were significantly older (65.2 +/- 14.7 vs 57.5 +/- 19, p<0.0001) (Table V). Furthermore, ALI C19+ patients were more likely to be male (64% vs 45%, p<0.0001) and more likely to be white (64% vs 59%, p=0.0199). However, a smaller proportion of ALI C19+ patients were Hispanic compared to COVID-19 patients without ALI (11% vs 15%, p<0.0001).

Furthermore, ALI C19+ patients had higher rates of primary hypertension (51% vs 40%, p<0.0001), atrial fibrillation and flutter (17% vs 10%, p<0.0001), Type 1 diabetes mellitus (5% vs 3%, p<0.0010), Type 2 diabetes mellitus (34% vs 22%, p<0.0001), chronic ischemic heart disease (28% vs 15%, p<0.0001), COPD (14% vs 8%, p<0.0001), nicotine dependence (18% vs 10%, p<0.0001), and psychiatric disorders (42% vs 35%, p=0.0026). However, ALI C19+ patients had lower rates of asthma compared to COVID-19 patients who did not develop ALI (7% vs 10%, p=0.0165).

ALI C19+ patients were more likely to be on baseline aspirin (35% vs 26%, p<0.0001), atorvastatin (29% vs 18%, p<0.0001), ACE inhibitors (20% vs 17%, p<0.0001), and Beta blockers (41% vs 30%, p=0.0003) than COVID-19 patients who did not develop ALI.

Outcomes of ALI C19+ patients compared to hospitalized C19+ patients without ALI

T-tests with propensity score matching were utilized. Following propensity matching for age, sex, ethnicity, comorbidities, and medications, ALI C19+ patients had higher 180-day rates of mortality (24.715% vs 14.449%, OR 1.944, p<0.0001), acute renal failure (22.053% vs 14.639%, OR 1.650, p=0.0019), respiratory failure or being placed on assisted ventilation (32.890% vs 26.996%, OR 1.325, p=0.0369), and sepsis (16.920% vs 12.167%, OR 1.470, p=0.0288) (Table

VI). Rates of stroke, myocardial infarction, and psychiatric complications were not significantly different.

DISCUSSION

Prior studies have demonstrated that SARS-CoV-2 is associated with a hypercoagulable state caused by virally-induced vascular endothelial injury.[5,12,13] Due to this procoagulant state, there is a high risk for macro- and micro-thrombi formation in COVID-19 patients.[13,14] Many of the thromboembolic events associated with COVID-19 are venous in nature but growing evidence has also shown an increased risk of arterial thrombotic events in COVID-19 patients, especially acute limb ischemia.[3,15–17] Galyfos et al utilized pooled data from multiple case studies to show that COVID-associated ALI presents in patients with low incidence of comorbidities and is associated with a high mortality and amputation risk, but their conclusions were limited by low sample sizes.[18] Using national data, our study demonstrates that ALI patients with COVID-19 face worse clinical outcomes compared to ALI patients without a COVID-19 diagnosis, suggesting that COVID-19 may not only precipitate ALI but may be directly responsible for exacerbating ALI sequelae.

Our analysis found that the demographics of patients who developed ALI following COVID-19 infection were significantly different from the characteristic demographics of those who presented with ALI alone. Because TriNetX displays aggregate data from institutions throughout the nation, the unmatched comparisons capture the trend that patients who developed ALI following COVID-19 had significantly higher rates of mortality, MALE, and acute renal failure despite lower rates of comorbidities. Even after propensity matching, we found that patients who developed ALI in the setting of COVID-19 had 2-fold higher rate of having MALE,

1.6-fold higher rate of having AKI, and 3.3-fold higher rate of death (Table II). While AKI and mortality are not unique to ALI, major adverse limb events are. We can say then that, independent of comorbidities, patients who developed ALI in the setting of COVID-19 have roughly 2-fold higher rates of major amputation compared to patients solely with ALI. These clinical outcomes are consistent with our understanding of how SARS-CoV-2 affects the vascular system and other organs. COVID-19 patients have been found to have abnormally elevated coagulation markers including D-dimer, partial thromboplastin time, prothrombin time, fibrinogen, fibrin degradation products, and IL-6.[5,15,19] Previous studies note that diffuse, small vessel platelet-fibrin thrombi and intravascular megakaryocytes were found in all major organs of COVID-19 patients, including the heart, lungs, kidney, liver, and mesenteric fat.[13] Menter et al also found that post-mortem examination of COVID-19 patients showed renal tubular injury, interstitial edema, and fibrin thrombi in glomerular capillaries.[20] Other studies have also illustrated vascular pathological changes such as vascular endothelial shedding, intimal inflammation, and thrombosis in COVID-19 patients.[21] In addition, in the United States, studies have previously shown that with increasing revascularization rates, amputations have drastically decreased in cases of critical limb ischemia.[22,23] Unfortunately, in the case of COVID-19 patients, amputation may have been the best treatment option due to delayed presentation to medical care or rapidly progressing disease.[24]

Finally, we found that rates of MALE, and acute renal failure were found to be higher in the ALI C19+ cohort that underwent arterial procedures than those without COVID-19 who underwent similar procedures. ALI C19+ patients also had higher rates of open reintervention (thromboendarterectomy, embolectomy, and/or thrombectomy) and bypass surgery. However, there was no difference in rate of endovascular reintervention between the groups. Successful

revascularization has been documented to be relatively low in COVID-19 patients compared with previously reported series.[3] Bellosta et al also postulated that their revascularization failure rate of almost 30% was due to the absence of forefoot microvasculature following intervention or potential sudden early recurrent thrombosis in their COVID-19 ALI patients. In addition, it is possible that poor clinical status of ALI C19+ patients prevented proper recovery following intervention, leading to post-operative complications. Early recognition of ischemic thrombotic events in COVID-19 patients and more aggressive anticoagulant and thrombolytic treatment may help prevent such serious adverse events in COVID-19 ALI patients.

Given that COVID-19 appears to exacerbate ALI sequelae, it was important to characterize the ALI C19+ population and compare it to hospitalized COVID-19 patients who do not develop ALI. Relative to hospitalized COVID-19 patients who do not develop ALI, ALI C19+ patients notably had higher rates of hypertension and diabetes mellitus. This is consistent with existing knowledge that hypertension and diabetes mellitus are main risk factors for limb ischemia[25]. Furthermore, development of ALI appears to suggest worse prognosis in patients with COVID-19. In addition to mortality and acute renal failure, development of ALI led to higher rates of respiratory failure or assisted ventilation, and sepsis.

There are certain limitations to this study. The TriNetX platform does not represent the general population, but rather only represents those who sought medical care at the 63 health care organizations in the network. Patients who do not receive follow-up care at participating healthcare organizations can also skew occurrence of outcomes. Propensity matching for some of our data set was limited by TriNetX's internal statistical analysis software and obfuscation policy. Safeguards against queries that could identify small subsets of cohorts are put in place to minimize the risk of patient re-identification.[26] There are also always inaccuracies inherent to

electronic health record data collection, mainly coding or data entry errors. We attempted to minimize any errors with strict inclusion and exclusion criteria, with particular focus on the temporality between the COVID-19 diagnosis and acute ischemic event. Lastly, the influence of thrombophylactic or therapeutic-anticoagulating regimes prior to development of ALI could not be assessed. As the pandemic progressed, many institutions developed their own guidelines with regards to stratifying patients with COVID-19 to receive thromboprophylaxis, therapeutic anticoagulation, or neither. Future studies should examine whether anticoagulation initiation in patients with COVID-19 prior to development of ALI affects outcomes.

CONCLUSIONS

Before and after controlling for covariates, rates of mortality, MALE, and acute renal failure were significantly higher in ALI C19+ patients than in patients with ALI alone. This suggests that COVID-19, independent of the patients' comorbidities, may directly exacerbate ALI sequelae. Furthermore, development of ALI suggests a worse prognosis in COVID-19 than in COVID-19 alone, with higher rates of mortality, renal failure, sepsis, and respiratory failure. Further studies are warranted to delineate a pathophysiologic link between COVID-19 and development of acute arterial thromboembolic events.

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Table I: Characteristics of patients who developed ALI from COVID-19 versus those who developed ALI without COVID-19			
	ALI C19+ (n=526)	**ALI (n=14131)**	**P-value**
Demographics			
Age	65.2 ± 14.7	65.6 ± 13.8	0.5109
Male	64%	59%	0.0534
Hispanic or Latino	11%	4%	**<0.0001**
Black/AA	16%	13%	0.0508
White	64%	69%	**0.0052**
Comorbidities			
Primary hypertension	51%	60%	**<0.0001**
Secondary hypertension	2%	2%	0.6972
Atrial fibrillation and flutter	17%	18%	0.6773
Type 1 diabetes mellitus	5%	4%	0.5260
Type 2 diabetes mellitus	34%	30%	**0.0420**
Overweight and obesity	19%	16%	0.1097
Chronic ischemic heart disease	28%	37%	**0.0001**
COPD	14%	20%	**0.0004**
Asthma	7%	7%	0.9350
Obstructive sleep apnea	7%	9%	0.2067
Nicotine dependence	18%	33%	**<0.0001**

Mental, Behavioral, and Neurodevelopmental disorders	42%	50%	**0.0004**
Neoplasms	19%	27%	**<0.0001**
Medications			
Aspirin	35%	49%	**<0.0001**
Atorvastatin	29%	38%	**<0.0001**
Simvastatin	6%	8%	0.1454
Losartan	12%	12%	0.8458
Oral hypoglycemic agents	15%	16%	0.2787
Anticoagulants	56%	56%	0.8458
ACE inhibitors	20%	29%	**<0.0001**
Beta blockers	41%	49%	**0.0003**

Table II: Outcomes of ALI in patients with COVID-19 and without COVID-19						
	Before propensity matching			**After propensity matching (for age, sex, ethnicity, comorbidities, and medications)**		
180-day outcomes	**ALI C19+, %, (n=526)**	**ALI, %, (n=14131)**	**Odds ratio, 95% CI; p-value**	**ALI C19+, %, (n=523)**	**ALI, %, (n=523)**	**Odds ratio, 95% CI; p-value**
Mortality	24.715 (130)	8.598 (1215)	**3.49 (2.838, 4.291); p<0.0001**	24.857 (130)	9.178 (48)	**3.273 (2.291, 4.678); p<0.0001**
Stroke	7.985 (42)	7.077 (1000)	1.139 (0.826, 1.572); p=0.4261	8.031 (42)	7.266 (38)	1.114 (0.706, 1.759); p=0.6417
Myocardial infarction	7.034 (37)	5.902 (834)	1.206 (0.857, 1.697); p=0.2808	7.057 (37)	5.163 (27)	1.399 (0.838, 2.333); p=0.1970
Major adverse limb event	5.894 (31)	2.696 (381)	**2.260 (1.550, 3.295); p<0.0001**	5.763 (30)	2.868 (15)	**2.061 (1.095, 3.878); p=0.0223**
Acute renal failure	22.053 (116)	13.347 (1886)	**1.837 (1.486, 2.270); p<0.0001**	22.180 (116)	14.914 (78)	**1.626 (1.184, 2.232); p=0.0025**

Table III: Outcomes of ALI patients with COVID-19 and without COVID-19, who initially underwent an arterial procedure for revascularization			
180-day outcomes	**ALI C19+, %, (n=89)**	**ALI, %, (n=2768)**	**Odds ratio, 95% CI; p-value**
Major adverse cardiovascular events (death, myocardial infarction, cerebral infarction)	25.843 (23)	19.725 (546)	1.418 (0.874, 2.300); p=0.1549
Major adverse limb events (amputation)	15.730 (14)	8.02 (222)	**2.141 (1.190, 3.850); p=0.0093**
Acute renal failure	22.472 (20)	14.884 (412)	**1.510 (1.016, 2.243); p=0.0492**
Reintervention-endovascular	17.978 (16)	13.403 (371)	1.416 (0.815, 2.459); p=0.2145
Reintervention-thromboendarterectomy, embolectomy, thrombectomy	31.461 (28)	4.986 (138)	**8.748 (5.418, 14.124); p<0.0001**
Reintervention-bypass	11.236 (10)	5.636 (156)	**2.119 (1.077, 4.173); p=0.0262**
*1:1 propensity matching was unable to be performed because of TriNetX's data obfuscation policy when patient sample sizes decrease below a specific threshold			

Table IV: Outcomes of ALI patients with COVID-19 and without COVID-19, who did not initially undergo an arterial procedure for revascularization			
180-day outcomes	**ALI C19+, %, (n=437)**	**ALI, %, (n=10186)**	**Odds ratio, 95% CI; p-value**
Major adverse cardiovascular events (death, myocardial infarction, cerebral infarction)	33.410 (146)	16.700 (1897)	**2.503 (2.039, 3.071); p<0.0001**
Major adverse limb events (amputation)	3.432 (15)	1.356 (154)	**2.586 (1.509, 4.433)l p=0.0003**
Acute renal failure	21.739 (95)	12.756 (1449)	**1.900 (1.504, 2.400); p<0.0001**
Intervention	2.746 (12)	5.573 (633)	**0.478 (0.268, 0.854); p=0.0108**
*1:1 propensity matching was unable to be performed because of TriNetX's data obfuscation policy when patient sample sizes decrease below a specific threshold			

Table V: Characteristics of COVID-19 patients who developed ALI versus hospitalized COVID-19 patients who did not develop ALI			
	C19 With ALI (n=526)	**C19 Without ALI (n=275903)**	**P-value**
Demographics			
Age	65.2 ± 14.7	57.5 ± 19	**<0.0001**
Male	64%	45%	**<0.0001**
Hispanic or Latino	11%	15%	**<0.0001**
Black/AA	16%	14%	0.1426
White	64%	59%	**0.0199**
Comorbidities			
Primary hypertension	51%	40%	**<0.0001**
Secondary hypertension	2%	1%	0.2644
Atrial fibrillation and flutter	17%	10%	**<0.0001**
Type 1 diabetes mellitus	5%	3%	**0.0010**
Type 2 diabetes mellitus	34%	22%	**<0.0001**
Overweight and obesity	19%	22%	0.0533
Chronic ischemic heart disease	28%	15%	**<0.0001**
COPD	14%	8%	**<0.0001**
Asthma	7%	10%	**0.0165**
Obstructive sleep apnea	7%	10%	0.0751

Nicotine dependence	18%	10%	**<0.0001**
Mental, Behavioral, and Neurodevelopmental disorders	42%	35%	**0.0026**
Neoplasms	19%	21%	0.2981
Medications			
Aspirin	35%	26%	**<0.0001**
Atorvastatin	29%	18%	**<0.0001**
Simvastatin	6%	5%	0.1454
Losartan	12%	9%	0.8458
Oral hypoglycemic agents	15%	13%	0.2787
Anticoagulants	56%	34%	0.8458
ACE inhibitors	20%	17%	**<0.0001**
Beta blockers	41%	30%	**0.0003**

Table VI: Propensity-matched outcomes of COVID-19 patients who developed ALI versus COVID-19 patients who did not develop ALI			
180-day outcomes	**ALI C19+, %, (n=526)**	**C19+, %, (n=526)**	**Odds ratio, 95% CI; p-value**
Mortality	24.715 (130)	14.449 (76)	**1.944 (1.421, 2.660); p<0.0001**
Stroke	7.985 (42)	5.323 (28)	1.543 (0.941, 2.530); p=0.833
Myocardial infarction	7.034 (37)	6.464 (34)	1.095 (0.676, 1.773); p=0.7124
Acute renal failure	22.053 (116)	14.639 (77)	**1.65 (1.201, 2.267); p=0.0019**
Mental health complications	17.300 (91)	14.449 (76)	1.239 (0.889, 1.726); p=0.2057
Respiratory failure or Assisted ventilation	32.890 (173)	26.996 (142)	**1.325 (1.017, 1.727); p=0.0369**
Sepsis	16.920 (89)	12.167 (64)	**1.470 (1.039, 2.080); p=0.0288**

Supplementary Table 1		
Outcome/Revascularization Procedure	**Corresponding ICD-10/Procedure code**	Notes
Mortality	Registered as deceased	
Stroke	I61-I63, G45.9	Ischemic and hemorrhagic stroke
Myocardial infarction	I21	
Major adverse limb events	1004982, 1005146, 1005298	Amputation procedures on pelvis, hip, femur, knee, leg and ankle joint
Acute renal failure	N17	
Major adverse cardiac events	Deceased, I61-63, G45.9, I21	Composite of death, stroke, and myocardial infarction
Respiratory failure or assisted ventilation	J96, 1014859	
Sepsis	A40, A41, R65.2	
Mental health complications	F43.1, F32, F33, G47, F41.1	PTSD, depressive episode, major depressive disorder (Recurrent), sleep disorders, generalized anxiety disorders

Reintervention	Composite of revascularization procedures	
Embolectomy or thrombectomy, with or without catheter	34151	renal, celiac, mesentery, aortoiliac artery, by abdominal incision
	34201	femoropopliteal, aortoiliac artery, by leg incision
	34203	popliteal-tibio-peroneal artery, by leg incision
Repair blood vessel, direct	35221	intra-abdominal
	35226	lower extremity
Repair blood vessel with vein graft	35251	intra-abdominal
	35256	lower extremity
	35281	intra-abdominal
	35286	lower extremity
Thromboendarterectomy, including patch graft, when performed	35302	Superficial femoral artery
	35303	Popliteal artery
	35304	Tibioperoneal trunk artery
	35305	tibial or peroneal artery, initial vessel
	35306	each additional tibial or peroneal artery
	35351	iliac
	35355	iliofemoral
	35361	combined aortoiliac
	35363	combined aortoiliofemoral
	35371	common femoral

	35372	deep femoral
Bypass graft, with vein:	35533	axillary-femoral-femoral
	35537	aortoiliac
	35538	aortobi-iliac
	35539	aortofemoral
	35540	aortobifemoral
	35556	femoral-popliteal
	35558	femoral-femoral
	35563	ilioiliac
	35565	iliofemoral
	35566	femoral-anterior tibila, posterior tibial, peroneal artery, or other distal vessels
	35570	tibial-tibial, peroneal-tibial, or tibial/peroneal trunk-tibial
	35571	popliteal-tibial, -peroneal artery or other distal vessels
In-situ vein bypass;	35583	femoral-popliteal
	35585	posterior tibial, or peroneal artery
	35587	popliteal-tibial, peroneal
Bypass graft, with other than vein;	35621	axillary-femoral
	35623	axillary-popliteal or -tibial
	35637	aortoiliac
	35638	aortobi-iliac

	35646	aortobifemoral
	35647	aortofemoral
	35654	axillary-femoral-femoral
	35656	femoral-popliteal
	35661	femoral-femoral
	35663	ilioiliac
	35665	iliofemoral
	35666	femoral-anterior tibial, posterior tibial, or peroneal artery
	35671	popliteal-tibial or peroneal artery
Arterial Mechanical Thrombectomy	37184	Primary percutaneous transluminal mechanical thrombectomy, noncoronary, non-intracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injection(s); initial vessel
	37185	Primary percutaneous transluminal mechanical thrombectomy, noncoronary, non-intracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injection(s); initial vessel; second and all subsequent vessel(s) within the same vascular family

	37186	Secondary percutaneous transluminal thrombectomy (eg, nonprimary mechanical, snare basket, suction technique), noncoronary, nonintracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injections, provided in conjunction with another percutaneous intervention other than primary mechanical thrombectomy
Revascularization, endovascular, open or percutaneous, iliac artery, unilateral, initial vessel;	37220	with transluminal angioplasty
	37221	with transluminal stent placement(s), includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, iliac artery, each additional ipsilateral iliac vessel;	37222	with transluminal angioplasty
	37223	with transluminal stent placement(s), includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral;	37224	with transluminal angioplasty
	37225	with atherectomy, includes angioplasty within the same vessel, when performed
	37226	with transluminal stent placement(s), includes angioplasty within the same vessel, when performed

	37227	with transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel;	37228	with transluminal angioplasty
	37229	with atherectomy, includes angioplasty within the same vessel, when performed
	37230	with transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37231	with transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, tibial/peroneal artery, unilateral, each additional vessel	37232	with transluminal angioplasty
	37233	with atherectomy, includes angioplasty within the same vessel, when performed
	37234	with transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37235	with transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed

Supplementary Table II: Covariates used in propensity matching	
Covariate	Notes
Age	
Sex	
Ethnicity	
Comorbidities	Primary hypertension, secondary hypertension, atrial fibrillation, T1DM, T2DM, Overweight/obesity, chronic ischemic heart disease, COPD, asthma, obstructive sleep apnea, nicotine dependence, mental/behavioral/neurodevelopmental disorders, neoplasms
Medications	Aspirin, atorvastatin, simvastatin, losartan, oral hypoglycemic agents, anticoagulants, ACE inhibitors, Beta blockers

Figure I: Propensity Score Density Function of ALI C19+ versus ALI Before Matching

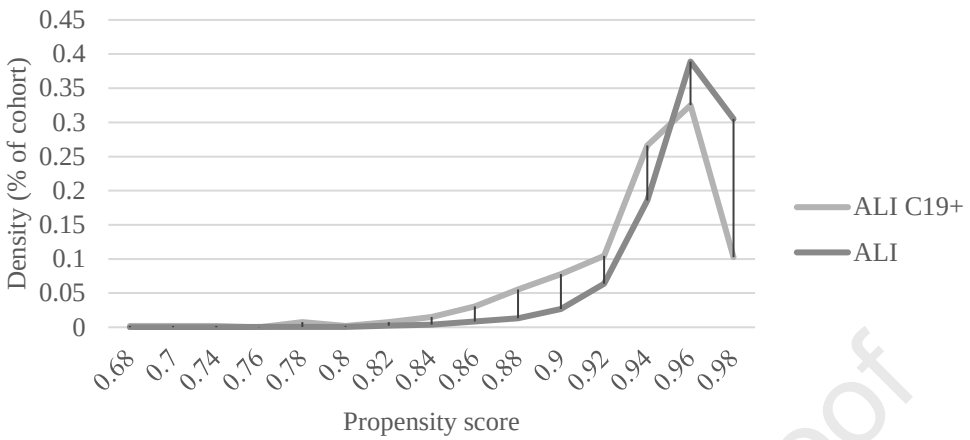

Figure II: Propensity Score Density Function of ALI C19+ versus ALI After Matching